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Cardiovascular magnetic resonance in Rheumatology: Current Status, Recommendations, use

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**Cardiovascular magnetic resonance in Rheumatology:****Current Status and Recommendations for use**

Sophie I Mavrogeni 1, George D. Kitas 2, Theodoros Dimitroulas 3, Petros P. Sfikakis 4, Philip Seo 5, Sherine Gabriel 6, Amit R. Patel 7, Luna Gargani 8, Stefano Bombardieri 9, Marco Matucci-Cerinic 10, Massimo Lombardi 11, Alessia Pepe 12, Anthony H. Aletras 13, Genovefa Kolovou 1, Tomasz Miszalski 14, Piet van Riel 15, AnneGrete Semb 16, Miguel Angel Gonzalez-Gay 17, Patrick Dessein 18, George Karpouzas 19, Valentina Puntman 20, Eike Nagel 20, Konstantinos Bratis 21, Georgia Karabela 22, Efthymios Stavropoulos 22, Gikas Katsifis 22, Loukia Koutsogeorgopoulou 23, Albert van Rossum 24, Frank Rademakers 25, Gerald Pohost 26, Joao A. C. Lima 27

1 Onassis Cardiac Surgery Center, Athens, Greece

2 Arthritis Research UK Epidemiology Unit, Manchester University, Manchester, UK

3 Department of Rheumatology, Dudley Group NHS Foundation Trust, Russells Hall Hospital, Dudley, West Midlands, DY1 2LT, UK

4 First Department of Propeudeutic and Internal medicine, Laikon Hospital, Athens University Medical School, Athens, Greece

5 Department of Rheumatology, John's Hopkins Hospital, Baltimore, Maryland, USA

6 Department of Medicine (Rheumatology) and Epidemiology, Mayo Clinic, Rochester, MN, USA

7 University of Chicago, Department of Medicine, Chicago, Illinois USA

8 Institute of Clinical Physiology - National Research Council, Pisa, Italy

9 Division of Rheumatology, Department of Clinical and Experimental Medicine,  
University of Pisa, Pisa, Italy.

10 Experimental and Clinical Medicine, Division of Internal Medicine and  
Rheumatology, Azienda Ospedaliera Universitaria Careggi, University of Florence,  
Florence, Italy

11 Multimodality Cardiac Imaging Section, Policlinico San Donato, Milano – Italy.

12 Magnetic Resonance Imaging Unit, Fondazione G. Monasterio C.N.R, Pisa, Italy

13 Laboratory of Computing and Medical Informatics, Department of Medicine, Aristotle  
University of Thessaloniki, Thessaloniki, Greece

14 Department of Internal Medicine, Jagiellonian University Medical College, Kraków,  
Poland

Center for Diagnosis, Prevention and Telemedicine, John Paul II Hospital, Kraków,  
Poland

Department of Clinical Radiology and Imaging Diagnostics, 4th Military Hospital,  
Wroclaw, Poland

15 Department of Rheumatology, Radboud University Medical Centre, Radboud,  
The Netherlands

16 Preventive Cardio-Rheuma clinic, Dept Rheumatology, Diakonhjemmet Hospital,  
Oslo, Norway

17 Health Research Institute of Santiago de Compostela (IDIS), Division of  
Rheumatology, Clinical University Hospital of Santiago de Compostela, Santiago de  
Compostela, Spain

18 Cardiovascular Pathophysiology and Genomics Research Unit, School of Physiology,  
Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

19 David Geffen School of Medicine-UCLA Chief, Division of Rheumatology, London,  
UK

20 University Hospital Frankfurt, Frankfurt, UK

21 King's College, London, UK

22 Athens Naval Hospital, Athens, Greece

23 Department of Pathophysiology, School of Medicine, University of Athens, Athens,  
Greece

24 Dept Cardiology, VU University Medical Center, Amsterdam, the Netherlands

25 Dept Cardiology, University Hospitals Leuven, Leuven, Belgium

26 Department of Cardiology, University of South California, LA, USA

27 Department of Medicine, Radiology and Epidemiology Johns Hopkins University,  
Baltimore, Maryland, USA

**All authors have been involved in the research, writing and/or substantial  
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**Address for correspondence:**

Sophie Mavrogeni, MD FESC

50 Esperou Street, 175-61, P. Faliro, Athens, Greece

Tel/Fax: +30-210-98.82.797, E-mail: soma13@otenet.gr

## Abstract

Targeted therapies in connective tissue diseases (CTDs) have led to improvements of disease-associated outcomes, but life expectancy remains lower compared to general population due to emerging co-morbidities, particularly due to excess cardiovascular risk.

Cardiovascular Magnetic Resonance (CMR) is a noninvasive imaging technique which can provide detailed information about multiple cardiovascular pathologies without using ionizing radiation. CMR is considered the reference standard for quantitative evaluation of left and right ventricular volumes, mass and function, cardiac tissue characterization and assessment of thoracic vessels; it may also be used for the quantitative assessment of myocardial blood flow with high spatial resolution and for the evaluation of the proximal coronary arteries. These applications are of particular interest in CTDs, because of the potential of serious and variable involvement of the cardiovascular system during their course.

The *International Consensus Group on CMR in Rheumatology* was formed in January 2012 aiming to achieve consensus among CMR and rheumatology experts in developing initial recommendations on the current state-of-the-art use of CMR in CTDs. The present report outlines the recommendations of the participating CMR and rheumatology experts with regards to: (a) indications for use of CMR in rheumatoid arthritis, the spondyloarthropathies, systemic lupus erythematosus, vasculitis of small, medium and large vessels, myositis, sarcoidosis (SRC), and scleroderma (SSc); (b) CMR protocols, terminology for reporting CMR and diagnostic CMR criteria for assessment and quantification of cardiovascular involvement in CTDs; (c) a research agenda for the further development of this evolving field.

## INTRODUCTION

The application of new treatment strategies, including targeted therapies in the connective tissue diseases (CTDs) has resulted in significant reduction of disease-associated mortality. However, life expectancy in CTDs remains lower compared to the general population (1), predominantly due to excess cardiovascular risk (2-6). Cardiac abnormalities in CTDs reflect various pathophysiologic mechanisms, such as systemic and vascular inflammation, accelerated atherosclerosis, myocardial ischemia due to impaired micro- or macrovascular circulation, abnormal cardiac vessel reactivity, myocardial fibrosis, cardiotoxic therapies and cardiac amyloid deposition (7-8). Heart involvement in CTDs remains silent and progresses gradually; once it becomes clinically overt, patients may present with advanced signs of heart failure and an ominous prognosis. (9). This makes the need for tools enabling early diagnosis of cardiovascular involvement even more pressing in the CTDs.

In the clinical arena, echocardiography, nuclear techniques and X-ray coronary angiography still remain the cornerstones of cardiac imaging; however, they have serious limitations in the early diagnosis of cardiac involvement in CTDs (10-16).

Cardiovascular Magnetic Resonance (CMR) is a noninvasive, imaging technique of great importance for the evaluation of the cardiovascular system. It does not use ionizing radiation, and therefore, allows for repeated scans over time. It has been successfully used in the diagnostic assessment of diseases of the great vessels, congenital heart diseases, iron overload, valvular and pericardial diseases, cardiomyopathies, coronary artery disease, heart failure, and myocardial inflammation (17-30). The capability of CMR to perform myocardial tissue characterization (oedema, fat,



infiltration, fibrosis) and ischemia detection holds serious promise for the preclinical diagnosis of heart involvement in CTDs.

The limitations of the currently used non-invasive techniques to detect early cardiac involvement in CTDs, emphasize the role of CMR as a valuable diagnostic tool in the field. The *International Consensus Group on CMR in Rheumatology* was founded in January 2012 to achieve consensus among CMR and rheumatology /cardiologist experts and develop recommendations on the current use of CMR in CTDs. Although guidelines about the CMR applications in cardiology have been already published by EuroCMR, the potential additive value of CMR in CTDs has not been clarified. The present report summarises existing evidence and the group's recommendations, which include: CMR protocols, terminology for reporting CMR findings, and diagnostic CMR criteria for assessment as well as quantification of cardiovascular involvement in CTDs and a research agenda for the further development of this evolving field.

## METHODS

The *International Consensus Group on CMR in Rheumatology* group was initially created by a core group including 3 cardiologists (SM, GP, JL), experienced in cardiac disease of CTDs, and well trained in CMR and 3 rheumatologists (GDK, PPS, TD) with a special clinical and research interest in cardiac disease of CTDs and good understanding of cardiac imaging in order to discuss the early diagnosis of heart involvement in CTDs, using currently available non-invasive techniques.

The core group used a questionnaire to address various clinical queries regarding the role of cardiovascular imaging in the early detection of heart involvement in CTDs.

Ideas, thoughts and suggestions of the core group were then further discussed with other colleagues with a demonstrable interest and expertise in the field, who eventually formed the *International Consensus Group on CMR in Rheumatology*. Group members reviewed the existing evidence about pathophysiology of heart disease in CTDs, the advantages and disadvantages of currently used non-invasive techniques and the potential utilisation of CMR to clarify those aspects of cardiac pathophysiology in CTDs that remain obscure using currently available diagnostic techniques. The decision-making process followed to formulate the recommendations and any inclusion and/or exclusion criteria was based on interaction between the group members via electronic communication and teleconferencing. Two members of the core group (SM and TD) collated all the responses and drafted various versions of the recommendations. These were initially reviewed, and if necessary amended by the other members of the core group. The resulting documents were circulated to the rest of the group members for detailed comment, further changes, if necessary, and final approval.

## **WHAT IS CMR?**

CMR images are derived from signals produced by protons (hydrogen nuclei) present in abundance in the human body. The main sequences used in CMR are shown in Table 1 (31).

### ***Contraindications and safety considerations***

In CMR, contrast agents are used for the detection of inflammation, fibrosis or myocardial ischemia consisting of chelates of gadolinium. Although there is no evidence of direct nephrotoxicity, some agents have been linked to systemic fibrosis (known as nephrogenic systemic fibrosis), provoking skin fibrosis, tendons contractures, joint immobility, internal organ involvement and finally death. Nephrogenic systemic fibrosis occurs in patients with glomerular filtration rate of  $<30$  ml/min/1.73 m<sup>2</sup> or patients on hemodialysis. However no new cases have been reported with some of the newer generations of gadolinium and particularly after the implementation of specific recommendations (32).

Patients with prosthetic heart valves, sternal wires, prosthetic replacements can be safely scanned. Retained epicardial pacing leads, or intracoronary stents can be also safely scanned, but at the moment there is no international consensus on the different methods to accomplish this. In patients with permanent pacemakers, automated implantable cardiac defibrillators or ferro-magnetic cerebrovascular aneurysm clips CMR is traditionally contraindicated (34). However, new magnetic resonance -safe or magnetic resonance -conditional devices are available and are recommended in cases likely to require serial CMR evaluations, such as cardiac sarcoidosis (35).

Although there is no known risk for use of this imaging technique during pregnancy, it is recommended that CMR is avoided during the first trimester. Chelates of gadolinium should not be used, as no data are available on possible teratogenic effects. Breastfeeding women must discard their milk for 24h after contrast agent injection (31, 34) although, there is no evidence to suggest harm to the infant or the mother (36).

### *Indications for CMR*

Current indications of CMR in CTDs are presented in Table 2

## **CARDIOVASCULAR INVOLVEMENT IN CTD**

### *Atherosclerosis and coronary artery disease*

Atherosclerosis-driven pathology is more prevalent in patients with CTDs than in the general population and is thought to be the main contributor to the increased cardiovascular mortality observed in these diseases (42-44). Traditional cardiovascular risk factors, such as hypertension, dyslipidemia and insulin resistance are more prevalent in many of the CTDs (7), but they are not sufficient to explain the magnitude of the increased (cardiovascular disease) CVD risk (45-49). Given that the inflammatory-immune underpinnings of atherosclerosis and (rheumatoid arthritis) RA share many similarities, it has been proposed that a chronic inflammatory state has proatherogenic effects on the vascular wall, leading initially to endothelial dysfunction. Indeed, RA, the spondyloarthropathies (SpAs), systemic lupus erythematosus (SLE), antiphospholipid syndrome and the vasculitides have all been associated with accelerated atherosclerosis (50-54). Particularly in RA, in which the risk for coronary artery disease is similar in magnitude to the risk conferred by diabetes mellitus (55), atherosclerotic plaques are often clinically silent and have an increased propensity to instability and rupture (56), leading to higher re-infarction rates with worse outcomes from acute coronary syndromes (57). The important role of systemic inflammatory burden in CVD is further supported by observations demonstrating improvement in CVD risk with potent anti-inflammatory therapeutic strategies in RA (58). While the precise relationship between systemic

inflammation and atherosclerosis remains to be determined, immune dysregulation, genetic predisposition and immunosuppressive treatment may contribute to increased CVD risk in CTDs (59).

### ***Myocardial dysfunction and heart failure***

Heart failure – whether or not related to ischemic heart disease – also accounts for the widening mortality gap between CTDs and the general population (60). In RA the prevalence of heart failure is two-fold higher than that in the general population, representing a major contributor to mortality (61). Clinical and subclinical impairment of myocardial function has been detected in a wide range of CTDs, including RA, SLE, systemic sclerosis (SSc), SpA and vasculitis (62-65). Notably, global indices of cardiac function such as left ventricular ejection fraction, lack sensitivity and cannot precisely assess the extent of myocardial dysfunction in CTDs, which usually present with diastolic dysfunction and a relatively low prevalence of systolic abnormalities (66-70). The risk for heart failure remained unchanged after adjusting for classical CVD risk factors and ischemic heart disease (71). Therefore, it is thought that these changes may reflect the effect of inflammation on myocardial remodeling, suggesting that the mechanisms of heart failure in CTDs are strongly linked to immune and adaptive pathways shared by CTDs and CVD. In addition, inflammation may affect the autonomic nervous system and thus elevate the heart rate, leading to lowering the time for diastolic filling and increasing cardiac workload, which in turn contributes to the impaired myocardial perfusion in CTDs (72). Furthermore, cardiomyopathy due to fibrosis and/or vascular changes is highly prevalent in systemic sclerosis, vasculitis, myositis and sarcoidosis, leading to impaired myocardial function and diastolic heart failure (73). However, similarly to RA,

left ventricular systolic function remains normal, and only new imaging modalities can identify cardiac abnormalities at a preclinical state (74, 75).

### ***Myocardial and vascular inflammation***

Inflammatory myocardial disease characterised by immune cell infiltration, degeneration and necrosis of cardiomyocytes, is a rare but high-risk and probably significantly underestimated cardiac complication of CTDs. Autoimmune myocarditis is more common in SLE and contributes significantly to CVD morbidity in other conditions such as vasculitis, sarcoidosis and inflammatory myopathies (76). Symptoms are not specific and usually the diagnosis is delayed, resulting in irreversible cardiac injury with potent life-threatening complications (77).

Many CTDs are associated with inflammation of large, medium and small blood vessels, resulting in intimal hyperplasia and occlusion that may produce ischemic manifestations such as stroke, myocardial infarctions, visual abnormalities, limb/jaw claudication and digital ulcers (78). Regardless of the vascular territory involved, the vasculitic lesions contribute to the increased prevalence of CVD with increased mortality. Vasculitis may cause cardiac ischemia, if located in epicardial coronary arteries, in small intramural cardiac vessels, or in the aorta (27,79).

### ***Pulmonary hypertension***

Depending on the exact disease, pulmonary arterial hypertension (PAH) affects 0.5-15% of patients with CTDs, is associated with worse prognosis and has lower therapeutic response than idiopathic PAH. PAH is most commonly seen in systemic

sclerosis and is responsible for almost 30% of disease-related deaths (80). Several underlying processes such as obstructive proliferative vasculopathy, chronic hypoxemia, due to interstitial lung fibrosis and pulmonary veno-occlusive disease have been identified as major contributors of increased pressure and vascular resistance in the pulmonary circulation (81). Despite advances in diagnostic modalities, almost 50% of CTDs with PAH are diagnosed when right heart disease has already progressed to advanced stages (82).

## **APPLICATIONS OF CMR IN CTD**

### ***Coronary artery disease and atherosclerosis***

#### **CMR detection of ischemia**

Myocardial ischemia in CTDs can be due either to coronary artery disease, as in SLE and RA, or due to microvascular dysfunction, as in primary or secondary small vessel vasculitis (14, 27). CMR detects ischemia by two different ways.

First, by observation of wall motion abnormalities induced by an inotropic agent such as dobutamine (83,84). However, due to the high prevalence of microvascular disease in CTDs, which cannot be differentiated from epicardial coronary artery disease by wall motion imaging, dobutamine stress CMR is less frequently used in CTD patients; it may, however, serve as an alternative to vasodilator perfusion imaging in patients with contraindications to contrast agents or vasodilator stress.

Second, by observation of myocardial perfusion using the first pass of a T1-shortening contrast agent (first-pass myocardial contrast enhancement) (85,86). Data

acquired during intravenous vasodilator-induced hyperemia (adenosine most commonly but also dipyridamole) delineate the underperfused regions, due to a lack of vasodilator reserve. The spatial resolution of CMR is 2-3 mm x 2-3 mm in-plane, greatly superior to nuclear techniques, allowing for a better identification of subendocardial ischemia (85,86). The interpretation is most commonly visual, but quantitative approaches are also available and have been validated against x-ray angiography, SPECT, and PET (85-90).

### ***CMR in microvascular disease***

Patients, usually women, with signs and symptoms of ischemia and no obstructive coronary artery disease often have coronary microvascular dysfunction, which carries an adverse prognosis. The gold standard for diagnosis is invasive coronary reactivity testing. Traditional noninvasive stress imaging maybe suboptimal to reveal this entity. CMR can be used as an non-invasive alternative to detect coronary microvascular dysfunction in this population (91,92). In CTDs, impairment of myocardial microcirculation is one of the primary events during the progression of cardiac disease particularly in SSc but also in other disease settings such as myositis, SLE and vasculitis. Diffuse disturbance of the myocardial microvasculature due to structural and functional abnormalities of small coronary arteries and arterioles results amongst others in repetitive ischaemic episodes with intermittent myocardial hypoperfusion contributing to patchy, myocardial fibrosis reported in studies employing CMR (93,94).



### ***CMR detection of fibrosis***

CMR is the reference standard for *in vivo* detection and quantification of myocardial scar/fibrosis and can be used to assess the underlying aetiology of heart failure. Importantly, not only ischaemic scar, but also scar due to myocarditis and non-ischaemic cardiomyopathy can be detected and frequently provides a specific diagnosis (95).

Both acute and old scars retain contrast agent and appear *bright* (96). The preferred imaging time for scar detection is 15-20 minutes after gadolinium administration, when differences between scar, normal myocardium, and blood pool are maximal; therefore, it is referred to as late gadolinium-enhancement (LGE).

Noninvasive assessment of myocardial viability can be performed by PET, SPECT, and Dobutamine echocardiography (97,98). However, different techniques assess myocardial viability according to different patterns. Stress echocardiography and CMR assess viability as contractile reserve, SPECT as myocardial perfusion defect and contrast CMR as myocardial scar. The great advantage of CMR is its ability to assess myocardial viability with different parameters within the same examination using only one cardiac imaging modality, that is LGE and contractile reserve and in the future with metabolic markers also (<sup>13</sup>C-CMR). Additionally, CMR can detect infarction in as little as 1 cm<sup>3</sup> of tissue, substantially less than in other methods (97,98) and facilitates diagnosis of small myocardial scars and diffuse subendocardial fibrosis, missed by other imaging techniques (14). Finally, CMR can differentiate between ischemic (subendocardial or transmural LGE pattern, following the distribution of coronary arteries) (Figure 1) and non-ischemic myocardial fibrosis (patchy, subepicardial or

intramyocardial LGE not following the distribution of coronary arteries) (Figure 2). Comparison between stress CMR and other stress techniques for detection of myocardial ischemia-fibrosis is shown in Table 3.

Myocardial perfusion defects have been already detected in 40% of women with SLE, using nuclear techniques. Early myocardial perfusion defects were also identified by CMR in sarcoidosis, RA and SSc and coexisted with normal coronary arteries in the majority of cases (99-101).

LGE, undiagnosed by echocardiographic or nuclear techniques, has been described in vasculitis (14, 25-27, 79, 102 – 112), myositis (113-117), SLE (13, 76, 118-125), RA (13, 27, 125-133), sarcoidosis (125, 134-138) and SSc (125, 139-149). LGE in CTDs does not present the typical pattern found in ischemic heart disease (subendocardial or transmural lesion in the territory supplied by the occluded vessel). However, the possibility of coronary artery disease should always be excluded, when evaluating these patients.

Novel CMR methods such as T1 mapping can add more diagnostic value in detecting subtle forms of myocardial fibrosis. The addition of post-contrast T1 mapping to pre-contrast T1 mapping acquisitions allows the calculation the gadolinium partition coefficient and the extracellular volume fraction of the myocardium provided that there is a steady-state equilibrium between the blood pool and the interstitium (150).

Given that diffuse myocardial fibrosis could be missed by traditional LGE imaging where the entire myocardium may be affected more homogeneously, as occurs with SSc, T1 mapping and extracellular volume quantification can provide a more reliable surrogate estimation of cardiac tissue. This concurs with recent studies

demonstrating subclinical heart disease in the form of myocardial fibrosis and inflammation in patients with SSc and RA (37-39).

### ***Heart failure (HF)***

#### **Measurement of LV volumes and ejection fraction**

CMR measures ventricular volumes and ejection fraction (EF) noninvasively and without a contrast agent. Echocardiography is still the everyday workhorse for bedside evaluation, but CMR has excellent reproducibility and the ability to accurately evaluate right ventricular morphology and function, which is of special interest in CTDs (151). A direct comparison of CMR versus echocardiography has shown that for an 80% power and a  $p$  value of 0.05, the sample size required would be 505 patients for validation of LV mass using 2D echo, but only 14 patients for CMR (152). Recently, a great enthusiasm developed on applying of 3D Echo for evaluation of volumes and ejection fraction; however Crean et al demonstrated statistically significant and clinically meaningful differences in right ventricular volumetric measurements between 3D Echo and CMR in adults with congenital heart disease, proving the CMR superiority (153).

CMR is an important tool in assessing heart failure aetiology (ischemic or nonischemic), extent of myocardial ischemia, amount of dysfunctional but viable myocardium as well as acute tissue injury (154,155). Recently, LGE was proven highly effective in detecting the mechanism of cardiac dysfunction in patients with newly diagnosed heart failure of unclear aetiology, as frequently happens in SLE (156) and RA (120-133). It is also clinically effective and economically viable as a gatekeeper to coronary angiography. Additional information is provided regarding biventricular

assessment and likelihood of benefit from device therapy (157), which has been recently applied to CTDs (158).

### ***CMR detection of oedema***

Myocardial oedema is a feature of acute myocardial injury, associated either with inflammation or with myocardial infarction. Oedema alters myocardial T2-relaxation and can therefore be detected by T2-weighted CMR imaging (159,160). It is important in CTDs, because it allows the detection of *cardiac disease acuity* (76-79, 102-107), which can potentially necessitate additional anti-rheumatic and/or cardiac medication.

T2-weighted or oedema imaging has been used to assess heart disease acuity in CTDs (13, 14, 76-79, 102-107, 119-133). Positive T2-weighted images are indicative of myocardial oedema during the acute phase of myocarditis and/or infarction and can be identified simultaneously or early before the appearance of LGE (123). Recently, the retrospective evaluation of CMR from 246 patients with connective tissue diseases with typical or atypical cardiac symptoms revealed abnormal CMR in 32 % (chronic 27%) and 15 % (chronic 12%) respectively. Lesions due to vasculitis, myocarditis and myocardial infarction were evident in 27.4%, 62.6% and 9.6% of CTDs, respectively. Stress studies in CTDs with negative CMR revealed coronary artery disease in 20% (125).

Despite improvement in T2 imaging over the last years detection of myocardial oedema remains challenging, due to limitations of the currently used T2-weighted dark-blood sequences. Recently introduced quantitative T1 and T2 mapping are different highly sensitive approaches for detection of myocardial water that allow the differentiation of oedematous from non-oedematous myocardium, based on absolute

values instead of differences in relative signal intensities (161). In fact T1 mapping may have superior performance to T2 mapping for the detection of acute myocardial oedema (162). The employment of these techniques provides a discrete quantification of myocardial oedema and inflammation which has improved sensitivity to detect myocarditis in various conditions including CTD, myocardial infarction and amyloidosis (38, 39, 163-168)

### ***Coronary magnetic resonance angiography (MRA) evaluation of coronary arteries***

Coronary MRA can be used to exclude 3-vessel disease and describe the proximal course of the coronary arteries (169-172). Although coronary artery computed angiography is considered the best way for fast non-invasive assessment of coronary arteries, coronary MRA has the advantage of lack of radiation, which is very important in young patients (173-177). However, coronary MRA has limitations in assessing the presence and severity of coronary artery disease due to very low diagnostic accuracy of this method.

Indications for coronary MRA include diagnosis of the anomalous origin of coronary arteries and evaluation of coronary artery ectasia or aneurysm as in Kawasaki disease and other vasculitides (25-27). Coronary MRA allows not only for initial diagnosis but also noninvasive, nonradiating follow up of these patients that can be achieved neither by coronary artery computed angiography nor by X-Ray coronary angiography (178).

The combination of coronary MRA with LGE allows simultaneous evaluation of coronary arteries and myocardial scar, which is the most important risk factor for major cardiac events and mortality (25-27).

### ***MRA evaluation of large and peripheral vessels***

Recent innovations in CMR offer the possibility of assessing the structure and function of the large and peripheral vessels particularly in patients with systemic vasculitis where early recognition and treatment of inflammatory or stenotic lesions in the aorta, pulmonary arteries, subclavian or other peripheral arteries are crucial for the reduction of CVD morbidity and mortality (113-119). Peripheral MRA has been successfully used in Behcet's disease (179), Takayasu arteritis, (29, 180-186) and adult-onset Still's disease (187).

### ***Myocardial, pericardial, endocardial and vascular inflammation***

#### ***Myocardial inflammation***

Myocarditis (autoimmune or infective) can manifest in different clinical scenarios varying from severe hemodynamic collapse to subclinical disease, undetectable by standard blood inflammatory markers and can potentially lead to dilated cardiomyopathy (188). Additionally, autopsy studies revealed that myocarditis is responsible for 5 to 20 % of sudden deaths in young adults and therefore early diagnosis is of great importance (189).

According to data coming from infective myocarditis, during early stages, it may remain undetected by echocardiography because this technique is unable to distinguish tissue structural changes (oedema, cell infiltration) that may occur initially without associated changes in LVEF. In myocarditis, a decrease in LVEF may not be initially evident, while an increase in cardiac troponin was found in only 20% of infective myocarditis (190). Additionally, myocardial biopsy, according to ACC/AHA guidelines, should be kept only for patients with unexplained new-onset heart failure of < 2 weeks in duration associated with a normal-sized or dilated LV with haemodynamic compromise and should not be used for screening or as a follow-up tool and is limited by sampling error and variation in observer expertise (191). However, similar data about autoimmune myocarditis are not currently available, maybe due to silent clinical presentation of myocarditis in the majority of these patients

CMR diagnoses myocarditis using three types of images: T2-weighted (T2W), early T1-weighted images (EGE) taken 1 min after injection of the contrast agent, and LGE images taken 15 minutes after the injection. T2-W is an indicator of tissue water content, which is increased in inflammation or necrosis such as myocarditis and myocardial infarction (Figure 2). To enhance the detection of pathologic alterations on CMR, images should be obtained early and late after gadolinium injection. Higher levels of EGE are due to increased membrane permeability or capillary blood flow. LGE is the third parameter, which should be also evaluated (Figure 3). Myocardial necrosis in the acute phase plays a major role in LGE formation. A combined CMR approach, using T2W in addition to EGE and LGE has a sensitivity of 76%, a specificity of 95.5%, and a diagnostic accuracy of 85% for the detection of myocardial inflammation (192).

In a study with both CMR and biopsy, histologically active myocarditis was found in 19 out of 21 patients with biopsy coincident with the area of LGE, but in only one patient in which the biopsy region did not coincide (192). In addition to LGE, other CMR sequences, such as EGE and oedema imaging using T2-weighted images can be of diagnostic value. In another study, CMR alone diagnosed 80% of patients with chest pain, positive necrosis enzymes, and absence of coronary artery disease and the diagnostic accuracy was improved when CMR was combined with endomyocardial biopsy (95% of patients were diagnosed) (193). In a study comparing CMR accuracy and histological findings in an animal model of myocarditis, it was documented that the topographic distribution of LGE and histological inflammation seem to influence sensitivity, specificity, positive and negative predictive values. Nevertheless, positive predictive value for LGE of up to 85% indicates that endomyocardial biopsy should be performed "MR-guided". LGE seems to have greater sensitivity than endomyocardial biopsy for the diagnosis of myocarditis (194). LGE can also offer prognostic information in patients with myocarditis. In a recent work including more than 200 patients with biopsy-proven myocarditis and CMR, LGE was the best independent predictor of both all-cause and cardiac mortality, with a hazard ratio superior to that of functional class, EF, or LV volumes (195).

Increasing amount of evidence demonstrates that T1 mapping may perform as well, if not better than the other CMR indices listed above even when it is used as a single imaging modality (162-164) (Figure 4).

CMR has been used for the evaluation of vasculitis (14, 25-27, 79, 102-112), myositis (113-119), SLE (13, 76, 120-125), RA (13, 27, 125-133), sarcoidosis (134-139)



and SSc (140-150). In many cases, CMR is thought to have identified cardiac disease acuity and myocardial inflammation-fibrosis, undetected by routinely used imaging techniques, thus facilitating risk stratification of the patients (125). Specifically, in cases of cardiac involvement in patients with idiopathic inflammatory myopathies (autoimmune myositis) the detection of myocardial involvement is hampered by a lack of sensitivity of traditional non-invasive methods, and the finding of elevated cardiac troponin T levels that may be due to regenerating skeletal muscle, rather than myocardial damage. In these cases, CMR is useful in the evaluation for the presence of myocarditis or alternative cardiac pathology (196).

CMR can also detect primary or secondary diffuse subendocardial vasculitis, commonly found in CTDs, which presents with a typical diffuse subendocardial fibrotic pattern (14) (Figure 5).

### ***Pericardial inflammation***

Pericarditis is the most common cardiac manifestation in SLE and to a lesser extent in RA, spondyloarthropathies, vasculitis, SSc, polymyositis, and sarcoidosis. Echocardiography is the ideal technique to diagnose pericarditis and to assess inflow patterns into right and left ventricle during inspiration and expiration, together with the flows in pulmonary and hepatic veins, thus differentiating constriction from restriction. However, CMR is helpful in providing additional information, including tissue characterization of the pericardium and myocardium. Using cine sequences, the pericardial effusion presents as a bright signal area and in the case of tamponade it is accompanied by RV compression. Monitoring of pericardial LGE is useful to assess

active pericarditis and treatment response. Constriction causes paradoxical motion of the interventricular septum, due to early RV filling, followed by LV filling with corresponding displacement of the septum to the RV in late diastole (34).

### ***Valvular and endocardial inflammation***

Valvular heart disease is common in CTDs. Antiphospholipid syndrome, either primary or secondary can lead to valvular abnormalities and lesions in the form of *nonbacterial vegetations, conducting mainly to mitral valve and less often to aortic valve regurgitation*. Antiphospholipid syndrome increases the risk for thromboembolic complications. Superimposed bacterial endocarditis can be rarely observed (197). In another study of 18-year follow-up of patients with RA, valvular disease was revealed in 7.9% and occurred more frequently in seropositive RA, with high disease activity despite treatment (198).

While echocardiography is the first-line imaging technique of heart valve disease, CMR is a valuable alternative in case of inconclusive results. Particularly, CMR allows quantification of aortic and pulmonary regurgitation and precise evaluation of the aorta and pulmonary arteries. Indications for CMR in valve diseases include pulmonary valve stenosis and regurgitation, aortic valve disease, mitral valve disease and tricuspid valve disease.

Detection of LGE is common in many valvular diseases, particularly in aortic stenosis, as part of the hypertrophic response. Several studies suggest that midwall fibrosis is an independent predictor of mortality in RA and ankylosing spondylitis (34).

### ***Pulmonary hypertension***

Although CMR is not used to diagnose PAH as right heart catheterization remains the gold standard for this procedure, it is an additional tool for the comprehensive evaluation of right ventricular function and structure by confirming features, adverse remodelling and complications of pulmonary hypertension (e.g. dilated right ventricle, right atrium and pulmonary trunk).

The ASPIRE registry, a study on the accuracy of CMR in PAH, proved that CMR is a useful alternative to echocardiography in the evaluation of PAH and supported a role for the measurement of left ventricular mass index, LGE and phase contrast imaging in addition to the right heart functional indices in CMR evaluation for suspected PAH (199) (Figure 6).

### **WHY USE CMR IN RHEUMATOLOGY?**

Although recent years have witnessed considerable advances in the management of patients with CTDs, premature mortality remains an unresolved and probably a neglected issue (200). Recent data suggests that decreased mortality rates between individuals with CTDs are more likely to be the reflection of improved survival in the general population rather than a result of better treatment (201, 202). Additionally, trends in overall and CVD mortality in CTDs have not significantly changed over the last decades (202, 203). As CVD disease holds a key role in reduced life expectancy observed in these conditions, the emphasis of rheumatology community is shifting from

characterization of the increased CVD burden towards the development of effective means of assessing, managing and reducing this excess risk.

For several years the cardiovascular manifestations of CTDs have been underdiagnosed and undertreated because of the occult nature and the different constellation of clinical signs which make the clinical evaluation more complex, the co-existence of features of systemic disease but more importantly the diagnostic uncertainties due to lack of reliable and validated diagnostic tools. It is worth noting that the chronic and relapsing nature of CTDs poses more difficulties in the diagnostic assessment of cardiovascular damage, as periods of active disease may result in acute inflammatory lesions over pre-existing areas of scar or fibrosis. To make things more complicated pre-assessment risk algorithms developed to aid the prediction of risk for CVD in general population and various other conditions appear to underestimate future CVD events in RA patients suggesting that additional tools should be incorporated in the CVD risk stratification and management in this population (204).

Currently, the most common noninvasive technique used in cardiac imaging is echocardiography, due to high availability, portability, low cost, lack of radiation and great expertise among cardiologists but cannot distinguish specific etiologies of global or regional myocardial dysfunction with accuracy. It is operator dependent, has the limitation of the acoustic window, cannot perform detailed tissue characterization and cannot define the type of tissue lesions in patients with preserved diastolic or systolic function (205). Particularly in CTDs, distinct pathologic processes affecting the myocardium may be identified by a more sensitive modality such as CMR allowing a better understanding of disease process. For example in SSc, where myocardial

involvement constitutes of inflammatory, fibrotic and microvascular components CMR has a greater sensitivity (75%) in detecting cardiac abnormalities compared to echocardiography (48%) (147). In cases with diastolic dysfunction, although a good correlation was observed between CMR and echocardiography, the latter is considered practically preferable to CMR, due to its simplicity and high availability (206).

Nuclear techniques currently used in cardiology practice for the evaluation of myocardial ischemia-fibrosis, have the disadvantages of high cost, radiation, inability to perform tissue characterization and low spatial resolution, not allowing the assessment of subepicardial, intramyocardial or subendocardial fibrotic lesions, frequently found in CTD (10).

Finally, X-Ray coronary angiography and endomyocardial biopsy are invasive techniques that can be used only in specific clinical indications (10, 11). The limitations of the currently available diagnostic techniques mentioned above are more important in the management of patients with CTDs because:

- CTDs usually have silent or oligosymptomatic cardiac presentation (27, 29)
- Myocarditis, frequently seen by histopathology in CTDs – with figures ranging from 100% in Kawasaki disease and other systemic vasculitides during the acute and even the convalescence phase, to 25–30% in inflammatory myopathies and SLE (76) - cannot be always detected by echocardiography (13)
- Diffuse, subendocardial vasculitis, either as primary or as secondary heart disease in CTDs and small epicardial, intramyocardial and subendocardial

fibrosis, due to inflammation or small myocardial infarction might not be detected either by echocardiography or by nuclear techniques (13, 14).

- Acuity of heart involvement cannot be detected by echocardiography or by nuclear techniques (13, 14).
- Large vessel angiography with simultaneous assessment of arterial wall inflammation cannot be performed either by echocardiography or nuclear techniques (29).
- Tissue characterization cannot be performed in an accurate and detailed way either by echocardiography or by nuclear techniques and cardiac CT (13, 14). These techniques may suggest the presence of potential lesions but do not provide definitive information.
- Most CTDs are in female patients who may not be able to perform exercise at adequate level, due to arthritis or muscular discomfort/weakness; therefore pharmacologic stress CMR, offering a noninvasive, non-radiating option, without the limitations of acoustic window and/or breast artefacts, may be the best technique for coronary artery and cardiac microvascular disease assessment in this population (15).

The rapid technological advances on cardiovascular imaging and the increasing number of therapeutic options for treatment of cardiovascular diseases led to an impressive development of highly sophisticated imaging techniques, such as CMR that has been proposed as an ideal technique for *myocardial structure, function, and viability*. Studies in different disease settings – SSc, RA, SLE - have revealed subtle forms of

myocardial inflammation and diffuse myocardial fibrosis as well as interstitial myocardial remodeling in asymptomatic patients with apparent normal heart function evaluated by echocardiography (37-41, 147). These observations suggest that subclinical involvement is associated with preserved global myocardial contractility although mild preclinical systolic and diastolic dysfunction was reported in SSc patients. Given the lack of sensitivity of conventional imaging modalities to capture early abnormalities in inflammatory heart disease during the preclinical phase, CMR can provide useful imaging biomarkers for the diagnostic evaluation and identification of high risk patients before ventricular dysfunction and irreversible myocardial injury occur. For example the detection of asymptomatic myocardial fibrosis in SSc may change the natural history of the disease by supporting an early vasodilatory therapeutic intervention – calcium channel blockers, angiotensin converting enzyme inhibitors or others- at the time that it is more likely to be effective. Furthermore extensive myocardial oedema and inflammation suggesting myocarditis and/or coronary vasculitis in acute, life threatening situations resolves diagnostic dilemmas in critically ill patients and provides the justification for important clinical decisions regarding the introduction of aggressive, immunosuppressive treatment. Although large perspective studies are missing there are a few reports highlighting the role of CMR as indicator of treatment efficacy too (108,114). Last but not least, CMR can be a valuable tool for addressing unresolved issues and questions such as whether systemic inflammatory activity is associated with myocardial inflammation and whether anti-rheumatic treatment influences CVD disease positively or negatively. In this regard a recently published study assessing cardiac function and

morphology by MRI showed improvement of myocardial remodeling and performance in RA patients following treatment with tocilizumab (207).

Guidelines about CMR application have been already recommended by the Society for Cardiovascular Magnetic Resonance (208).

Based on CMR applications proposed by Society for Cardiovascular Magnetic Resonance, CMR protocols for evaluation of CTDs were created and presented in Tables 4, 5.

## **RECOMMENDATIONS FOR USE OF CMR IN CTD**

CMR is a noninvasive, non-radiating imaging technique of special interest for assessment of CVD involvement in CTDs. It is the gold standard for the evaluation of: LV volumes, mass, ejection fraction of atria and ventricles; LA Structure and function; Myocardial inflammation; Myocardial ischemia-necrosis; Inflammation in large, medium and small arteries; and ectatic or aneurysmatic coronaries.

**We suggest that CMR should be considered as a potentially viable diagnostic tool for CTDs evaluation in the following cases:**

- To evaluate patients with acute or persistent typical or atypical cardiac symptoms and normal routine noninvasive evaluation.
- To evaluate the possibility of silent myocardial inflammation in inflammatory myopathies with normal routine noninvasive evaluation
- To clarify the myocardial status in scleroderma with acute symptoms and normal routine noninvasive evaluation



- To evaluate the possibility of myocardial and/or vascular inflammation in primary or secondary vasculitis
- To evaluate any CTD patient with acute LV dysfunction
- To evaluate any CTD patient with recent onset of RBBB, LBBB, atrioventricular block or evidence of arrhythmia with or without positive routine noninvasive evaluation
- To clarify the myocardial status in technically inconclusive routine noninvasive evaluation or in case that the results of this evaluation cannot explain the patients' symptoms and signs.
- When, although the systemic disease appears under control, the patient has typical or atypical cardiac symptoms and noninvasive cardiac evaluation is negative
- If the patients' symptoms suggest to commence or modify cardiac treatment and the routine noninvasive evaluation is normal or doubtful
- To assess stress myocardial perfusion in CTDs, unable to exercise, with poor acoustic window or increased breast size; additionally, in young CTDs in whom repeated radiation should be avoided
- As a gatekeeper for X ray coronary angiography in CTDs with cardiac symptoms and mild or abnormal echocardiographic findings

## Conclusions

In patients with CTDs, the assessment of CVD is now regarded as part of the global management along with controlling of disease activity and inflammation. The optimal management of CVD risk requires the prompt diagnosis of cardiovascular complications however a substantial number of individuals with impairment myocardial function remain unrecognized and recent thoughts suggest the need for enhancement of CV risk stratification and management with more sensitive approaches. CMR complementing the physician's clinical skills along with echocardiography can also be useful tools to identify high-risk patients requiring diligent surveillance and permit earlier intervention, potentially reducing the impact of myocardial dysfunction on cardiovascular morbidity and mortality in this population.

Although CMR appears a very exciting diagnostic tool for patients with CTDs its use is still in its infancy and for each question answered several more are generated. More importantly data from large prospective studies is lacking. The majority of studies to date have been small cross-sectional or even smaller longitudinal observation cohorts. Clearly more research focusing on specific cardiac endpoints and long term outcomes is warranted to determine whether CMR can improve our diagnostic and managing capabilities in CVD risk stratification in CTDs.

To date, CMR has helped uncover previously undetected (either clinically or through other investigations) cardiac disease in patients with CTD: the prognostic value of this information remains in most cases elusive; so does any hard evidence that intervention based exclusively on such findings is required, what intervention would be best for each pathology identified and what might be their risk/benefit ratio. A non-exclusive list of potential research directions includes:

- Fully characterise the CMR pattern of heart involvement in CTDs (acute/chronic phase, rest/pharmacologic stress, oedema, macro-microfibrosis) and correlate it with traditional and novel CVD risk factors and clinical findings.
- Assess the role of molecular imaging. Molecular imaging aims at characterization and quantification of molecular and cellular processes non-invasively within intact living organisms. To sense biological processes such as cell trafficking in vivo, imaging reporter agents that interact specifically with molecular targets and appropriate imaging systems are currently under development. In RA, they have been used to facilitate diagnosis and monitor therapeutic regimens, and support the development of new therapies (209).
- Future clinical trials are recommended to evaluate the CMR pattern of heart involvement before and after antirheumatic and cardiac treatment, especially in patients with CTDs and positive CMR, who have no cardiac symptoms or no other evidence of systemically active disease.

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Table 1. Summary of CMR techniques applied to image different heart conditions.

CMR techniques	Heart condition imaged
Multislice spin-echo	Morphology of the myocardium and fat; blood predominantly dark.

Multislice SSFP	Morphology of vascular compartments with blood predominantly bright.
Cine SSFP	Functional imaging of wall motion, assessment of volumes and ejection fraction, wall thickness/thickening
Cine SSFP with tissue tagging	Myocardial deformation, strain torsion. Pericardial constriction
First-pass contrast-enhancement	Myocardial perfusion. Myocardial ischemia.
First-pass contrast-enhancement With pharmacological stressor	Myocardial ischemia
T1-weighted	Fat tissue: pericardial, lipomatous metaplasia in myocardial scar.
T2-weighted	Myocardial edema associated with inflammation or acute myocardial infarction.
T2-star (T2*)	Myocardial iron deposition

Late gadolinium enhancement	Focal replacement fibrosis (scar). In acute infarction: area of necrosis. Infiltration (e.g. amyloid)
Native T1-mapping	Myocardial disease involving myocyte plus interstitium Myocardial oedema/fibrosis
T2-mapping	Oedema quantification
T1-mapping with use of extracellular contrast agent	ECV, interstitium, diffuse fibrosis.

ECV= extracellular volume fraction      SSFP= steady-state free precession.

Table 2. Current indications of CMR in CTDs

CV disease acuity
Myocarditis
Myocardial infarction
Vasculitis
Myocardial stress-rest perfusion

Myocardial fibrosis-infiltration
Microvascular disease
Evaluation of coronary arteries, large and peripheral arteries
Assessment of biventricular function
Constrictive pericarditis
Evaluation of unexplained heart failure
Assessment of valvular heart disease (specifically quantification of mitral/aortic regurgitation)

Table 3. Comparison of different diagnostic approaches for detection of myocardial ischemia-fibrosis

	<b>Stress ECG</b>	<b>Stress Echo</b>	<b>Stress Nuclear</b>	<b>Stress CMR</b>
<b>Limitations</b>	Inability to exercise, poor results in intermediate risk pts and vasculitis	Poor acoustic window	Inability to detect small perfusion defects	CMR contraindications
<b>Scar detection</b>	N/A	Indirect, through wall motion changes	Inability to detect small or subendo-cardial scars	High
<b>Cost</b>	Low	Low	High	High
<b>Availability</b>	High	High	High	Low
<b>Spatial resolution</b>	N/A	Low	Low	High
<b>Artifacts</b>	N/A	High	High	Low
<b>Operator dependency</b>	Low	High	Low	Low
<b>Radiation</b>	No	No	Yes	No

Stress ECG= Stress electrocardiogram

Stress echo= Stress echocardiography

Stress Nuclear= Stress radionuclide techniques

Stress CMR= Stress cardiovascular magnetic resonance

Table 4. Proposed rest CMR protocol for CTDs evaluation

Parameter evaluated	CMR methodology for rest study (evaluation of myocarditis, heart failure, vasculitis, valvular disease, pericarditis)
Anatomy+Function	LVEDV, LVESV, LVEF, RVEDV, RVESV, RVEF, wall motion changes using SSFP.
Myocardial inflammation and/or necrosis	T2 STIR, early (EGE) and late (LGE) gadolinium (Gd) enhanced T1 images (according to JACC White paper) T1 and T2 mapping
Coronary arteries	Coronary MRA in Kawasaki disease
Large arteries	Aortic and pulmonary artery MRA, either with Gd, or by SSFP, if abnormal renal function. Aortic wall assessment using black-blood images.
Peripheral arteries	Peripheral arteries MRA using Gd

LVEDV= Left ventricular end-diastolic volume

LVESV= Left ventricular end-systolic volume

LVEF= Left ventricular ejection fraction

RVEDV= Right ventricular end-diastolic volume



RVESV= Right ventricular end-systolic volume

RVEF= Right ventricular ejection fraction

SSFP= Steady State Free Precession

T2 STIR= T2-weighted short tau inversion recovery

MRA=Magnetic resonance angiography

Table 5. Proposed stress CMR protocol for CTDs evaluation

Parameter evaluated	CMR methodology for stress study (evaluation of chest pain, wall motion or perfusion abnormalities, coronary micro-or macro-vascular disease)
Adenosine stress CMR perfusion	First-pass perfusion sequence: balanced Turbo Field Echo, TR 2.8 ms, TE 4 ms, FA 45, slice thickness 8 mm, preparation pulse delay 200 ms
Wall motion assessment using Dobutamine	Wall motion changes after Dobutamine, using SSFP sequence, if there are contraindications for adenosine (asthma, atrioventricular block.
Myocardial fibrosis	LGE assessment, using 3D-Turbo field echo sequence, TR 5.1 ms, TE 2.5 ms, FA 15, slice thickness 8 mm.

IR balanced Turbo Field Echo= Inversion recovery Turbo Field Echo

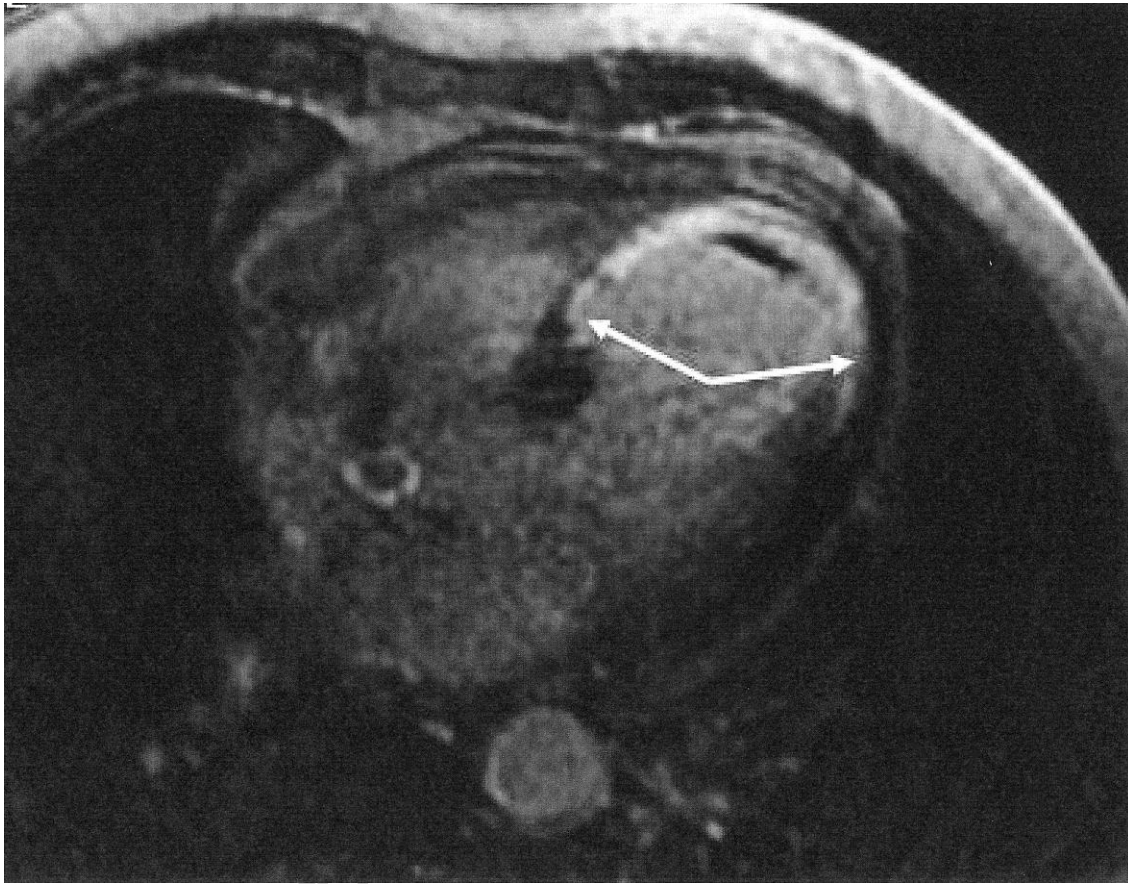
TR= Repetition time

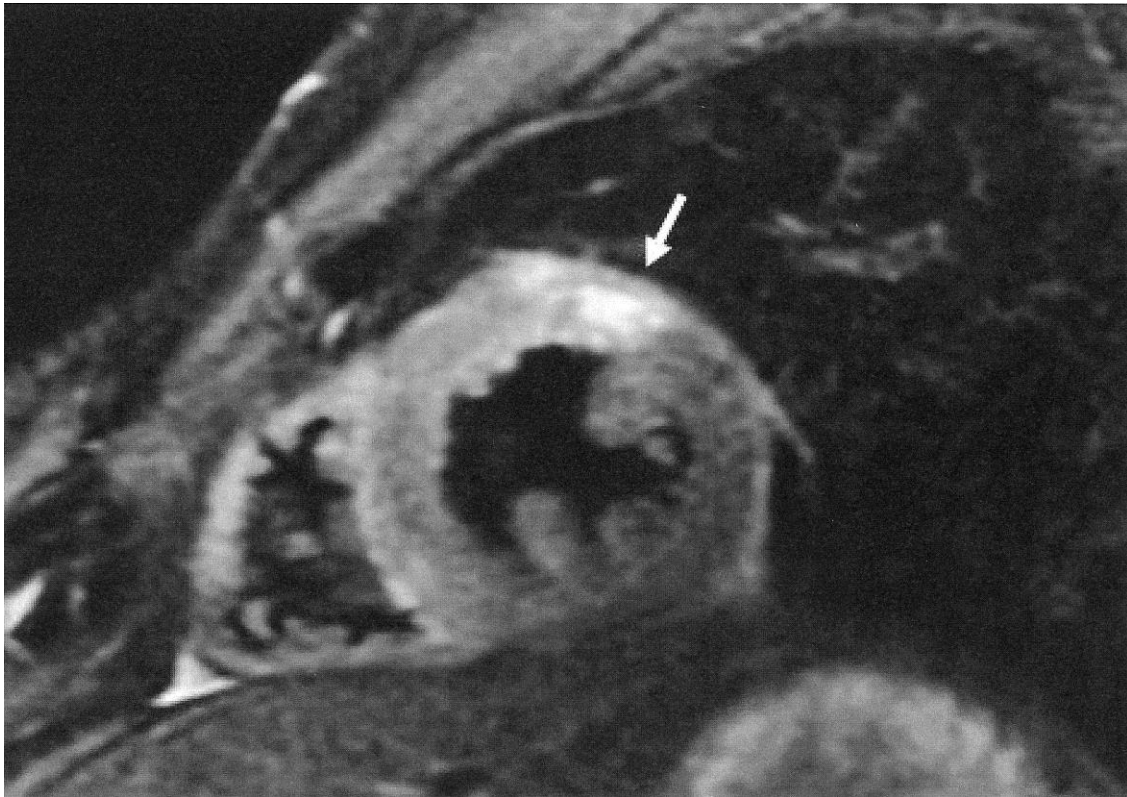
TE= Echo time

FA= Fractional anisotropy

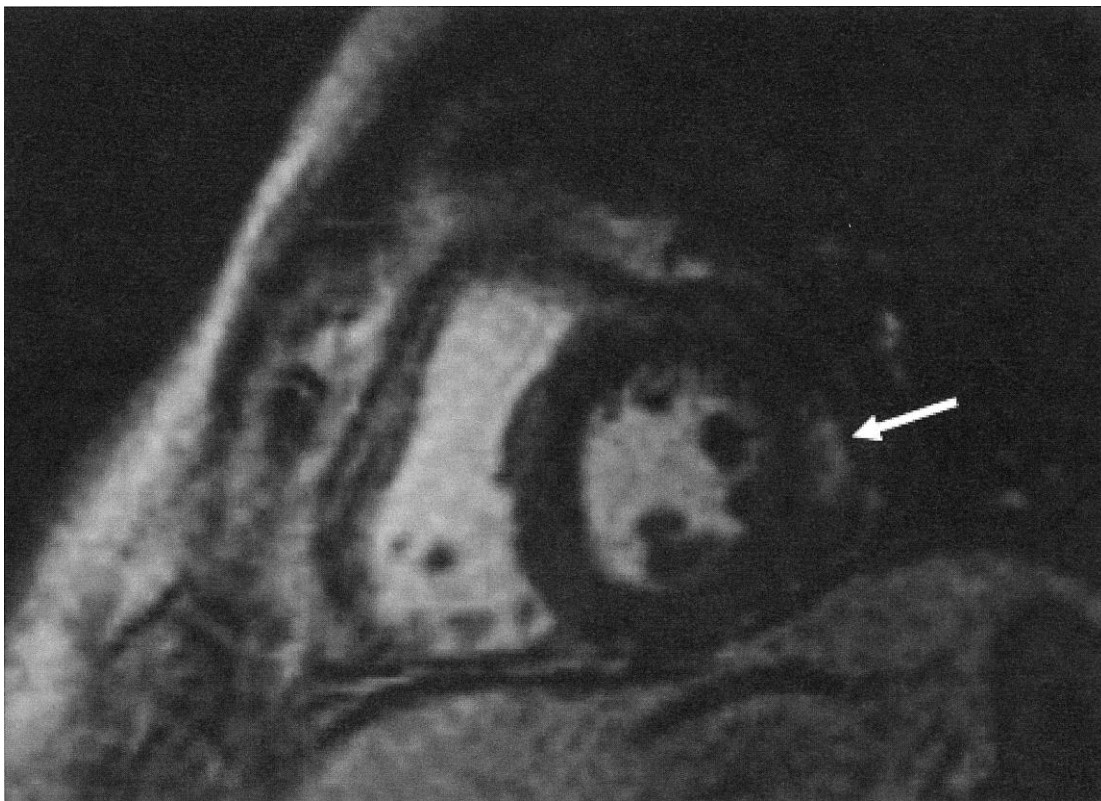
LGE= Late gadolinium enhancement

3D-Turbo field echo sequence= three dimensional balanced steady-state free precession sequence

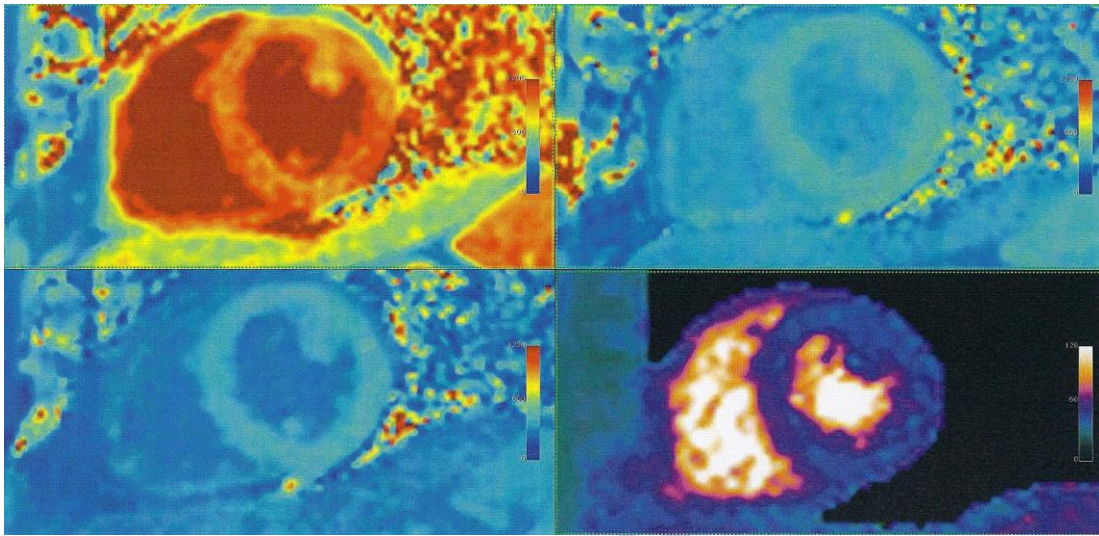
**Figures****Fig 1**

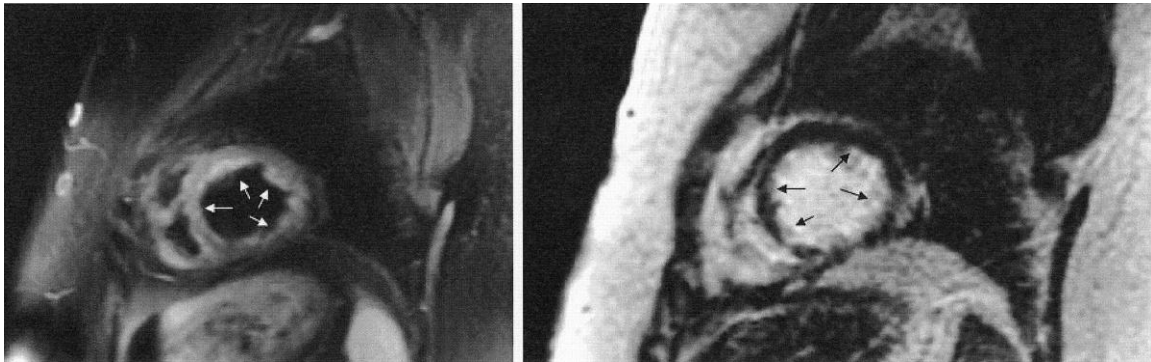


**Fig 2**

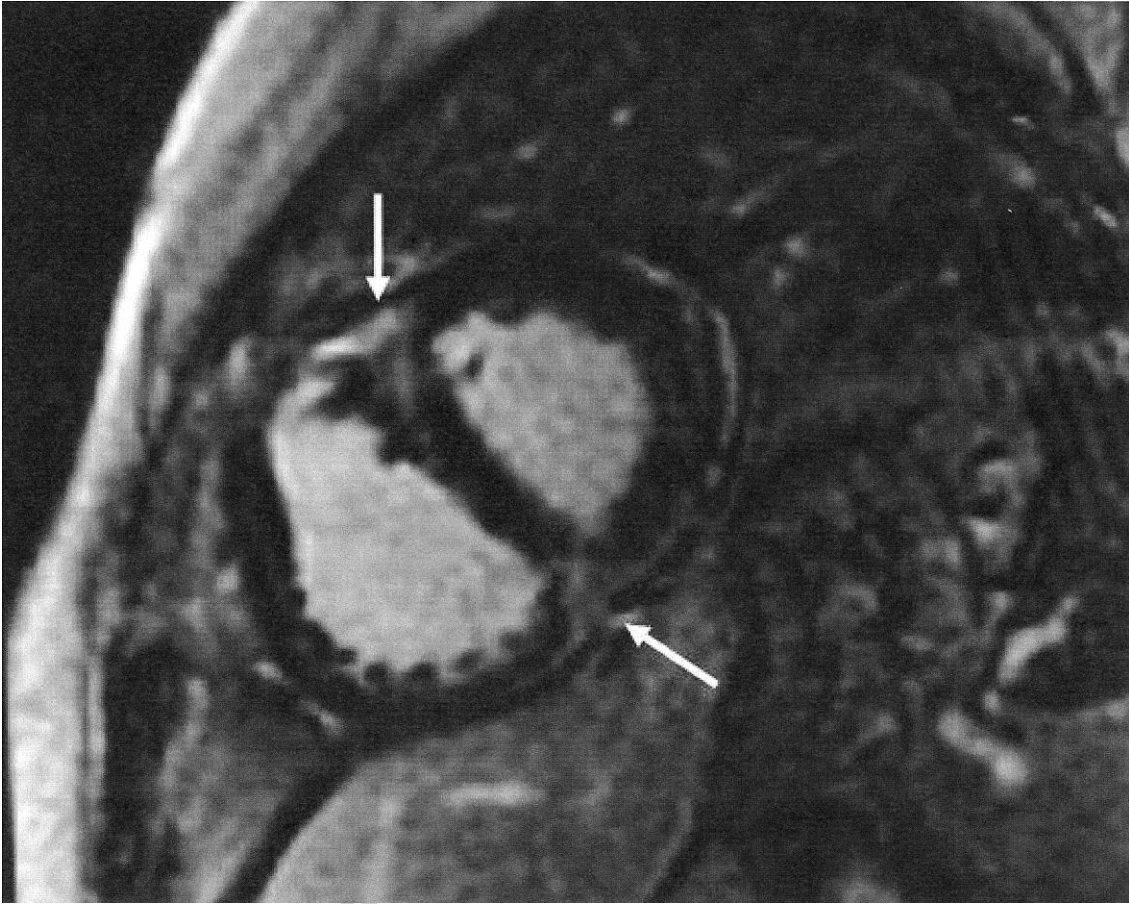


**Fig 3**

**Fig 4**



**Fig 5**



**Fig 6**



## Legends to figures

**Figure 1.** Subendocardial or transmural LGE following the distribution of coronary vessels (arrows) can be found, due to coronary artery disease or coronary vessels vasculitis. In this case, a transmural LGE in interventricular septum and LV apex, due to myocardial infarction after LAD occlusion, was identified in a patient with RA

**Figure 2.** Evidence of local oedema in the anterolateral wall of LV (arrow) can be detected by STIR T2 imaging during myocarditis

**Figure 3.** Patchy, intramural or subepicardial LGE (arrow), similar to viral myocarditis, as in this case, can be found either due to autoimmune myocardial inflammation or focal vasculitis, as in this case of a patient with SLE

**Figure 4.** Native T1, 25 min T1, T2 and 12 min T1 clockwise from top left, in a patient with sinus rhythm and heart failure with LVEF>35%.

**Figure 5.** Diffuse, subendocardial oedema (area indicated by arrow in the left image) and diffuse, subendocardial LGE (area indicated by arrow in the right image) not following the distribution of coronary arteries can be found either in primary or in secondary small vessel vasculitis as in this patient with Churg-Strauss syndrome

**Figure 6.** Patchy LGE at the insertion points and concurrent fluttering of intraventricular septum (arrows), due to pulmonary hypertension in a patient with SSc and PAH

**Highlights**

- CMR can evaluate symptomatic CTDs with normal routine noninvasive findings.
- CMR can exclude myocarditis and perform stress perfusion in CTDs, unable to exercise
- CMR can evaluate myocardial and/or vascular inflammation in vasculitis
- CMR can evaluate CTDs with LV dysfunction, block, arrhythmia or inconclusive tests
- CMR can be used in CTDs as a gatekeeper for coronary angiography